CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 064031

Trade Name : AMOXICILLIN CHEWABLE TABLETS

Generic Name: Amoxicillin Chewable Tablets

Sponsor : Novopharm, Ltd.

Approval Date: December 19, 1996

AADA 64-031

Novopharm Ltd.
U.S. Agent: Thérèse M. Ast, Ph.D., Esq.
Granutec, Inc.
4409 Airport Drive, N.W.
Wilson, NC 27896

Dear Madam:

This is in reference to your abbreviated antibiotic application dated March 30, 1992, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Amoxicillin Tablets USP (Chewable), 125 mg and 250 mg.

Reference is also made to your amendment dated November 20, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your 125 mg and 250 mg chewable tablets to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Amoxil® 125 mg and 250 mg chewable tablets of SmithKline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the

proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

12/15/95

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW NO.** 6

2. **AADA#** 64-031

3. **NAME AND ADDRESS OF APPLICANT**
Novopharm Limited
30 Nably Court
Scarborough, Ontario Canada M1B2K9

4. **LEGAL BASIS FOR AADA SUBMISSION**
21 CFR §440.103c - The application is based on the reference drug **Amoxil, Chewable Tablet®** manufactured by Smith Kline Beecham (AADA 50-542).

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Amoxicillin Tablets USP (Chewable)

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
N/A

9. **AMENDMENTS AND OTHER DATES**
Firm:
Original Submission: 3/31/92
Amendment: 10/14/92
Amendment: 2/16/94
Amendment: 8/14/95
Amendment: 7/16/96
Telephone Amendment: 8/27/96
Amendment: 11/20/96

FDA:
Refusal to File: 4/24/92
Acceptance to File: 5/7/92
Deficiency Letter: 7/13/92
Deficiency Letter (bio): 11/30/92
Deficiency Letter: 4/9/93
Deficiency Letter: 6/8/94
Deficiency Letter: 3/25/96
Deficiency Letter: 9/19/96

10. **PHARMACOLOGICAL CATEGORY**
Antibacterial

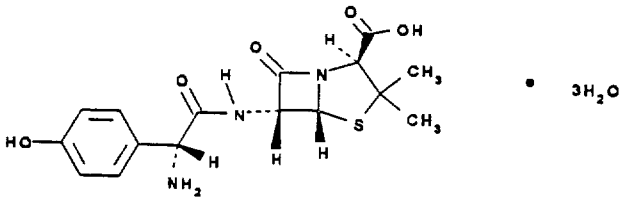
11. **HOW DISPENSED**
Rx

12. **RELATED IND/NDA/DMFs**

13. **DOSAGE FORM**
Tablets (chewable)
Proposed scoring is identical to the listed drug Amoxil®, 125 mg (unscored) and 250 mg (scored)

14. **STRENGTH**
125 mg; 250 mg

15. **CHEMICAL NAME AND STRUCTURE**



(1) 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-, trihydrate[2S-[2α,5α,6ß(S*)]]-;
(2) (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid trihydrate.

$C_{16}H_{19}N_3O_5S.3H_2O$
Molecular Weight: 419.46

16. **RECORDS AND REPORTS**
N/A

17. **COMMENTS**
Issues concerning the proposed impurity limits (release & stability) were resolved with the 11/20/96 amendment.

18. **CONCLUSIONS/RECOMMENDATIONS**
Recommend approval

19. **REVIEWER** Susan Rosencrance 12/11/96 **DATE COMPLETED** 12/10/96

AMOXICILLIN CAPSULES USP
250 mg and 500 mg

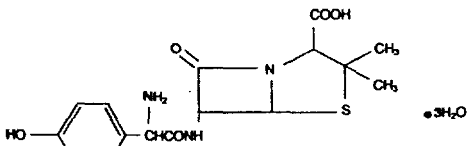
AMOXICILLIN FOR ORAL SUSPENSION
USP
125 mg/5 mL and 250 mg/5mL

AMOXICILLIN TABLETS USP,
CHEWABLE
125 mg and 250 mg

DESCRIPTION

Amoxicillin, USP is a semisynthetic antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many Gram-positive and Gram-negative microorganisms. Its chemical name is D-(-)-α-amino-p-hydroxybenzyl penicillin trihydrate.

The structural formula is:



Molecular Formula: $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$

Molecular Weight: 419.45

Each capsule for oral administration contains 250 mg or 500 mg amoxicillin (as the trihydrate). Each chewable tablet for oral administration contains 125 mg or 250 mg amoxicillin (as the trihydrate). After constitution, each 5 mL of suspension for oral administration contains 125 mg or 250 mg amoxicillin (as the trihydrate).

Inactive capsule ingredients include colloidal silicon dioxide, corn starch, magnesium stearate, and sodium lauryl sulfate.

Inactive chewable tablets ingredients include artificial cherry flavor, aspartame, colloidal silicon dioxide, D&C Red #30, FD&C Red #40, magnesium stearate, mannitol, microcrystalline cellulose, and sorbitol.

Inactive oral suspension ingredients include citric acid anhydrous, FD&C Red #40, methylparaben, propylparaben, sodium citrate hydrous, sucrose, and strawberry flavor. The 250 mg/5 mL suspension also contains colloidal silicon dioxide.

CLINICAL PHARMACOLOGY

Amoxicillin is stable in the presence of gastric acid and may be given without regard to meals. It is rapidly absorbed after oral administration. It diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. Amoxicillin is not highly protein-bound. In blood serum, amoxicillin is approximately 20% protein-bound as compared to 60% for penicillin G.

Orally administered doses of 250 mg and 500 mg amoxicillin capsules result in average peak blood levels one to two hours after administration in the range of 3.5 mcg/mL to 5.0 mcg/mL and 5.5 mcg/mL to 7.5 mcg/mL respectively.

Orally administered doses of amoxicillin suspension 125 mg/5 mL and 250 mg/5 mL result in average peak blood levels one to two hours after administration in the range of 1.5 mcg/mL to 3.0 mcg/mL and 3.5 mcg/mL to 5.0 mcg/mL respectively. Amoxicillin chewable tablets, 125 mg and 250 mg, produced blood levels similar to those achieved with the corresponding doses of amoxicillin oral suspensions.

Detectable serum levels are observed up to 8 hours after an orally administered dose of amoxicillin. Following a 1 gram dose and utilizing a special skin window technique to determine levels of the antibiotic, it was noted that therapeutic levels were found in the interstitial fluid. Approximately 60 percent of an orally administered dose of amoxicillin is excreted in the urine within six to eight hours.

MICROBIOLOGY

Amoxicillin is similar to ampicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. *In vitro* studies have demonstrated the susceptibility of most strains of the following Gram-positive bacteria: alpha- and beta-hemolytic streptococci, *Diplococcus pneumoniae*, nonpenicillinase-producing staphylococci, and *Streptococcus faecalis*. It is active *in vitro* against many strains of *Haemophilus influenzae, Neisseria gonorrhoeae, Escherichia coli* and *Proteus mirabilis*. Because it does not resist destruction by penicillinase, it is not effective against pe[illegible]illinase-producing bacteria, particularly resistant staphylococci. All strains of Pseud[illegible]monas and most strains of Klebsiella and Enterobacter are resistant.

DISC SUSCEPTIBILITY TESTS:

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to ampicillin-class antibiotics. Interpretations correlate diameters of the disc test with MIC values for amoxicillin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

*Bauer, A.W., Kirby, W.M.M., Sherris, J.C. and Turck, M.: *Antibiotic Testing by a Standardized Single Disc Method*, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

INDICATIONS AND USAGE

Amoxicillin is indicated in the treatment of infections due to susceptible strains of the following:

Gram-negative organisms - *H. influenzae, E. coli, P. mirabilis and N. gonorrhoeae.*

Gram-positive organisms - Streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinase-producing staphylococci.

Therapy may be instituted prior to obtaining results from bacteriological and sus[illegible] to determine the causative organisms and their susceptibility to

[illegible]tially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever or urticaria. The following adverse reactions have been reported as associated with the use of penicillins.

Gastrointestinal: Nausea, vomiting and diarrhea. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. **(See WARNINGS.)**

Hypersensitivity Reactions: Erythematous maculopapular rashes, erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis and urticaria have been reported.

NOTE: These hypersensitivity reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, amoxicillin should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to amoxicillin therapy.

Liver: A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

DOSAGE AND ADMINISTRATION

Infections of the ear, nose and throat due to streptococci, pneumococci, nonpenicillinase-producing staphylococci and *H. influenzae;*

Infections of the genitourinary tract due to *E. coli, Proteus mirabilis* and *Streptococcus faecalis;*

Infections of the skin and soft-tissues due to streptococci, susceptible staphylococci and *E. coli:*

USUAL DOSAGE:
Adults: 250 mg every 8 hours.
Children: 20 mg/kg/day in divided doses every 8 hours.
Children weighing 20 kg or more should be dosed according to the adult recommendations.
In severe infections or those caused by less susceptible organisms:
500 mg every 8 hours for adults and 40 mg/kg/day in divided doses every 8 hours for children may be needed.

Infections of the lower respiratory tract due to streptococci, pneumococci, nonpenicillinase-producing staphylococci and *H. influenzae:*

USUAL DOSAGE:
Adults: 500 mg every 8 hours.
Children: 40 mg/kg/day in divided doses every 8 hours.
Children weighing 20 kg or more should be dosed according to the adult recommendations.

Gonorrhea, acute uncomplicated ano-genital and urethral infections due to *N. gonorrhoeae* (males and females):

USUAL DOSAGE:
Adults: 3 grams as a single oral dose.
Prepubertal children: 50 mg/kg amoxicillin combined with 25 mg/kg probenecid as a single dose.

NOTE: SINCE PROBENECID IS CONTRAINDICATED IN CHILDREN UNDER 2 YEARS, THIS REGIMEN SHOULD NOT BE USED IN THESE CASES.

Cases of gonorrhea with a suspected lesion of syphilis should have dark-field examinations before receiving amoxicillin, and monthly serological tests for a minimum of four months.

Larger doses may be required for stubborn or severe infections.

The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults.

It should be recognized that in the treatment of chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller doses than those recommended above should not be used. Even higher doses may be needed at times. In stubborn infections, therapy may be required for several weeks. It may be necessary to continue clinical and/or bacteriological follow-up for several months after cessation of therapy. Except for gonorrhea, treatment should be continued for a minimum of 48 to 72 hours beyond the time that the patient becomes asymptomatic or evidence of bacterial eradication has been obtained. It is recommended that there be at least 10 days' treatment for any infection caused by hemolytic streptococci to prevent the occurrence of acute rheumatic fever or glomerulonephritis.

DIRECTIONS FOR MIXING ORAL SUSPENSION

Prepare suspension at time of dispensing as follows: Add the required amount of water for constitution (see table below) in two portions to the dry mixture in the bottle. Shake well after each addition.

125 mg/5 mL and 250 mg/5 mL

Bottle Size	Amount of Water Required for Constitution
80 mL	48 mL
100 mL	60 mL
150 mL	90 mL
200 mL	122 mL

Each teaspoonful (5 mL) will then contain after constitution either 125 mg or 250 mg amoxicillin.

After constitution, the required amount of suspension should be placed directly on the child's tongue for swallowing. Alternate means of administration are to add the required amount of suspension to formula, milk, fruit juice, water, ginger ale or cold drinks. These preparations should then be taken immediately. To be certain the child is receiving full dosage, such preparations should be consumed in entirety.

HOW SUPPLIED

Amoxicillin Capsules

Amoxicillin Capsules 250 mg are opaque caramel caps and opaque buff-colored bodies imprinted N and 250 on opposing cap and body portions.
724

Each capsule contains 250 mg of amoxicillin as the trihydrate. They are supplied as follows:

NDC 55953-724-27	unit of use bottles of 30.
NDC 55953-724-40	bottles of 100.
NDC 55953-724-70	bottles of 500.
NDC 55953-724-80	bottles of 1000.
NDC 55953-724-01	unit dose packages of 100.

Amoxicillin Capsules 500 mg are elongated opaque buff capsules imprinted N and 500 on opposing cap and body portions. 716

[illegible] 500 mg of amoxicillin as the trihydrate. They are supplied

*Bauer, A.W., Kirby, W.M.M., Sherris, J.C. and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972

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Gram-positive organisms - Streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinase-producing staphylococci.

Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reaction to any of the penicillins is a contraindication.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, APPROPRIATE THERAPY SHOULD BE INSTITUTED AND DISCONTINUANCE OF AMOXICILLIN THERAPY CONSIDERED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

USAGE IN PREGNANCY

Safety for use in pregnancy has not been established.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including amoxicillin, and may range in severity from mild to life-threating. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

As with any potent drug, periodic assessment of renal, hepatic and hematopoietic function should be made during prolonged therapy.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving Enterobacter, Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Phenylketonurics: Amoxicillin tablets USP, 125 mg chewable contain 2.90 mg of phenylalanine per tablet. Amoxicillin tablets USP, 250 mg chewable contain 5.79 mg phenylalanine per tablet.

ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essen-

Amoxicillin Capsules

Amoxicillin Capsules 250 mg are opaque caramel caps and opaque buff-colored bodies imprinted N and 250 on opposing cap and body portions.
724

Each capsule contains 250 mg of amoxicillin as the trihydrate. They are supplied as follows:

NDC 55953-724-27	unit of use bottles of 30.
NDC 55953-724-40	bottles of 100.
NDC 55953-724-70	bottles of 500.
NDC 55953-724-80	bottles of 1000.
NDC 55953-724-01	unit dose packages of 100.

Amoxicillin Capsules 500 mg are elongated opaque buff capsules imprinted N and 500 on opposing cap and body portions.
716

Each capsule contains 500 mg of amoxicillin as the trihydrate. They are supplied as follows:

NDC 55953-716-27	unit of use bottles of 30.
NDC 55953-716-33	bottles of 50.
NDC 55953-716-40	bottles of 100.
NDC 55953-716-70	bottles of 500.
NDC 55953-716-80	bottles of 1000.
NDC 55953-716-01	unit dose packages of 100.

Amoxicillin Tablets, Chewable

Amoxicillin Tablets 125 mg, chewable, are pink, round, convex, unscored chewable tablets engraved N on one side and 125 on the reverse.
747

Each tablet contains 125 mg of amoxicillin as the trihydrate. They are supplied as follows:

NDC 55953-747-35	bottles of 60.
NDC 55953-747-40	bottles of 100.
NDC 55953-747-70	bottles of 500.

Amoxicillin Tablets 250 mg, chewable, are pink, round, convex, scored chewable tablets engraved N on one side and 250 on the reverse.
751

Each tablet contains 250 mg of amoxicillin as the trihydrate. They are supplied as follows:

NDC 55953-751-35	bottles of 60.
NDC 55953-751-40	bottles of 100.
NDC 55953-751-70	bottles of 500.

Amoxicillin for Oral Suspension

Amoxicillin 125 mg/5 mL is supplied as follows:

NDC 55953-149-38	bottle size 80 mL.
NDC 55953-149-40	bottle size 100 mL.
NDC 55953-149-47	bottle size 150 mL.
NDC 55953-149-53	bottle size 200 mL.

Amoxicillin 250 mg/5 mL is supplied as follows:

NDC 55953-130-38	bottle size 80 mL.
NDC 55953-130-40	bottle size 100 mL.
NDC 55953-130-47	bottle size 150 mL.
NDC 55953-130-53	bottle size 200 mL.

STORAGE

Amoxicillin Capsules

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a well-closed container.

Amoxicillin Tablets, Chewable

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight containers as defined in the USP.

Amoxicillin for Oral Suspension

Prior to mixing store at controlled room temperature, 15°-30°C (59° -86°F). Refrigerate after mixing. Any unused portion must be discarded after 14 days. Keep tightly closed. SHAKE WELL BEFORE USING.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured by: Novopharm Limited,
Toronto, Canada M1B 2K9

Manufactured for: Novopharm USA Inc.,
Schaumburg, IL 60173

66832

Printed in U.S.A.
Revised April 1996
Rev. 01

N-000/AC

64-031

FPL

NDC 55953-747-35

60 TABLETS

Amoxicillin

Tablets USP, Chewable

125 mg

APPROVED

Caution: Federal law prohibits dispensing without prescription

novopharm

Each chewable tablet contains 125 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.
Manufactured by: Novopharm Ltd., Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot:

Exp: DEC 19 1996

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

66832LF-5835 Printed in Canada Rev. 00

0 12899 74735 5

NDC 55953-747-35

60 TABLETS

Amoxicillin

Tablets USP, Chewable

125 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

Each chewable tablet contains 125 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
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NDC 55953-747-35

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Amoxicillin

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125 mg

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novopharm

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Exp: DEC 19 1996

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Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

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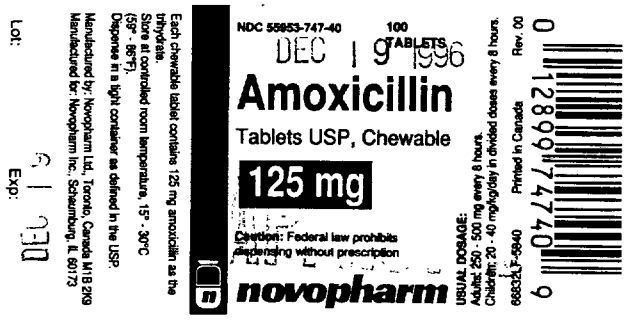
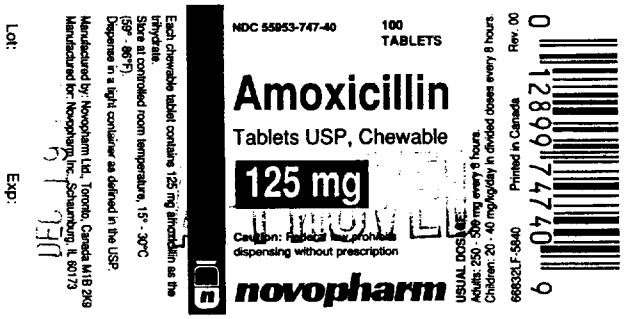
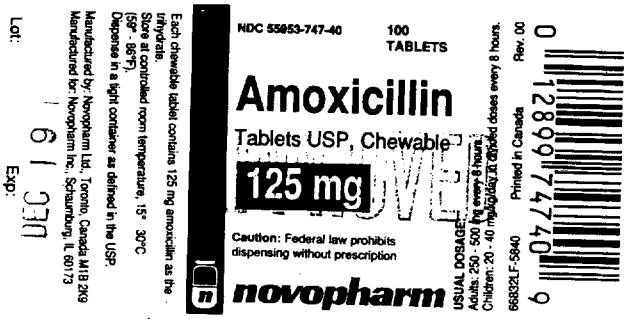
FPL







668331LA-5870 Printed in Canada Rev. 00

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

NDC 55953-747-70 500 TABLETS

Amoxicillin

Tablets USP, Chewable

125 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

Each chewable tablet contains 125 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.

Manufactured by: Novopharm Ltd.,Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot: Exp:

668331LA-5870 Printed in Canada Rev. 00

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

NDC 55953-747-70 500 TABLETS

Amoxicillin

Tablets USP, Chewable

125 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

Each chewable tablet contains 125 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.

Manufactured by: Novopharm Ltd.,Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot: Exp:

64-031
N-000/AC

Each chewable tablet contains 250 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a light container as defined in the USP.
Manufactured by: Novopharm Ltd., Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot:
Exp:

NDC 55953-751-35
60 TABLETS

Amoxicillin

Tablets USP, Chewable

250 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

66833LF-5835 Printed in Canada Rev. 00

0 12899 75135 2

Each chewable tablet contains 250 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a light container as defined in the USP.
Manufactured by: Novopharm Ltd., Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot:
Exp:

NDC 55953-751-35
60 TABLETS

Amoxicillin

Tablets USP, Chewable

250 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

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66833LF-5835 Printed in Canada Rev. 00

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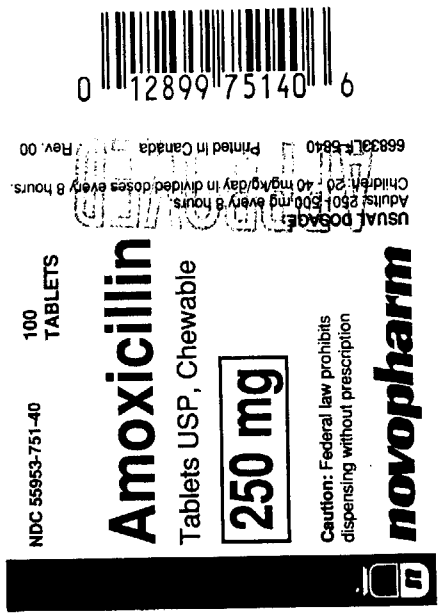
Caution: Federal law prohibits dispensing without prescription

novopharm

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

66833LF-5835 Printed in Canada Rev. 00

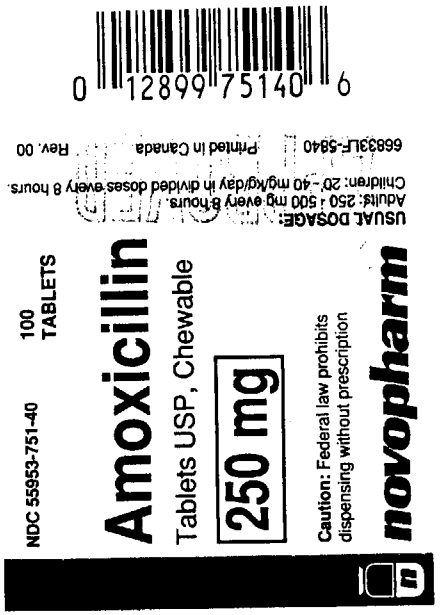
0 12899 75135 2



Each chewable tablet contains 250 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.

Manufactured by: Novopharm Ltd.,Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot: Exp:



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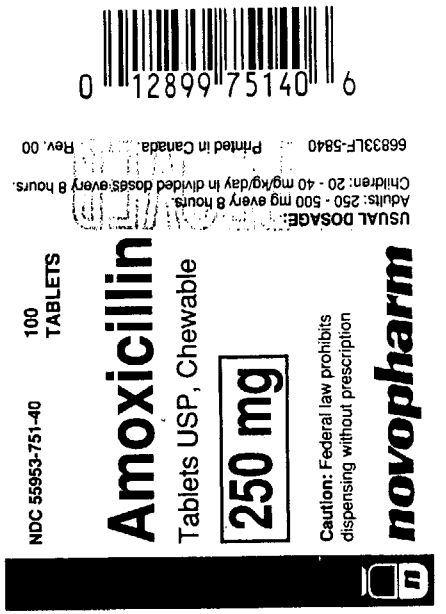
Manufactured by: Novopharm Ltd.,Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot: Exp:



Each chewable tablet contains 250 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.

Manufactured by: Novopharm Ltd.,Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot: Exp:

N-000/AC
LH-031

FPL

NDC 55953-751-70

500
TABLETS

Amoxicillin

Tablets USP, Chewable

250 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

66833LF-5870 Printed in Canada Rev. 00

0 12899 75170 3

Each chewable tablet contains 250 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.

Manufactured by: Novopharm Ltd., Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot:

Exp: DEC 19 1998

NDC 55953-751-70

500
TABLETS

Amoxicillin

Tablets USP, Chewable

250 mg

Caution: Federal law prohibits dispensing without prescription

novopharm

USUAL DOSAGE:
Adults: 250 - 500 mg every 8 hours.
Children: 20 - 40 mg/kg/day in divided doses every 8 hours.

66833LF-5870 Printed in Canada Rev. 00

0 12899 75170 3

Each chewable tablet contains 250 mg amoxicillin as the trihydrate.
Store at controlled room temperature, 15° - 30°C (59° - 86°F).
Dispense in a tight container as defined in the USP.

Manufactured by: Novopharm Ltd., Toronto, Canada M1B 2K9
Manufactured for: Novopharm Inc., Schaumburg, IL 60173

Lot:

Exp: DEC 19 1998

Amoxicillin Chewable Tablet
125 mg and 250 mg
Form 6, #64-031

NOV 30 1992

SPONSOR:
Novopharm LTD
30 Nably Court
Scarborough, ONT Canada

AGENT:
Dr. Thomas Kenyhercz
146 Flanders Drive
Hillsborough, NJ 08876

Dear Dr. Kenyhercz:

Reference is made to the in vivo bioequivalence study, dissolution data and waiver request which you submitted on March 30, 1992 in support of your amoxicillin chewable tablet.

The material has been reviewed by the Division of Bioequivalence and we have the following comments:

COMMENTS:

RECOMMENDATION:

The bioequivalence study conducted by for Novopharm Ltd. on its and amoxicillin 250 mg chewable tablet is incomplete per comments above.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
HFD-632 Pollock
HFD-650 (Dighe, Greenberg, CST)
stm 11-23-92 (A64031.STD)
bio letter

NOV 16 1992

Amoxicillin Chewable Tablet
125 mg and 250 mg
Form 6, #64-031
Reviewer: J. Lee
64031SDW.392

Novopharm Ltd.
Ontario, Canada
Submission date:
March 30, 1992

Review of an in-vivo Bioavailability Study, Dissolution Testing Data (2) and a Request for Waiver

Background

This submission represents the second bio-study for this drug product submitted by Novopharm Ltd. The first study (rev. dates: 8/7/90 and 10/22/91) was submitted under Form 6, #63-280 and contained many deficiencies as well as unacceptable dissolution testing results. The review of the chemistry portions of the submission also revealed a large number of deficiencies and the company opted to withdraw that application on October 29, 1991.

The company has resubmitted their application for their test product under #64-031.

Objective:

To assess the relative rate and extent of absorption of two formulations of amoxicillin 250 mg chewable tablet (Novopharm product vs Amoxil®) after administration in fasted subjects.

Study Design:

The clinical study (#1179-1) was conducted by
under the direction of

Twenty-four healthy, normal, non-smoking male volunteers (plus alternates) between the ages of 18-45 were successfully screened for the study. All were within ±10% of ideal body weight for his height and frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983.

The selected volunteers had normal findings in the pre-study physical examination; normal vital signs and ECG; urine sample free of drugs of abuse; clinical laboratory values (biochemical profile, hematology, and urinalysis) within ±10% of normal ranges, unless deemed clinically insignificant by the investigator.

Potential volunteers were excluded if they had:

1. History of hypersensitivity to amoxicillin or the penicillin class of drugs.

2. History or presence of cardiac, pulmonary, gastrointestinal, endocrine, neuromuscular, neurological, hematological, liver or kidney disease.

3. History of asthma, chronic bronchitis or other bronchospastic condition.

4. Any clinically significant illness during the four weeks prior to entry in this study.

5. Any significant physical or organ abnormality.

6. History of drug dependency or requires maintenance therapy with any drug.

7. Use of systemic medication (R_x or OTC) within 14 days prior to entry into the study.

The study was designed as a two-way, single-dose, randomized crossover with a one week washout period between dosings. The treatments consisted of a single (2 x 250 mg) dose of the following:

A. Amoxicillin
250 mg Chewable tablet (x2)
Novopharm Ltd., batch #PD 1867
expiry: November, 1993

B. Amoxil®
250 mg Chewable tablet (x2)
Beecham Laboratories, batch #RH2047
expiry: April, 1993

The dosing regimen for the volunteers was as follows:

	Period I	Period II
sequence I	A	B
sequence II	B	A

sequence I - subj. 2, 3, 4, 5, 6, 9, 10, 13, 18, 19, 23, 24, 25, 27, 28

sequence II - subj. 1, 7, 8, 11, 12, 14, 15, 16, 17, 20, 21, 22, 26

* Subjects #1-24 were the original enrollees for the study. Subjects #25, 26, 27 and 28 were entered as substitutes for subject dropouts. There were three additional subjects (# 29-31) that were screened for the study as extras but were dismissed from the study prior to onset. Subjects #2 and 25 withdrew from the study before its initiation. The protocol specifies 24 subjects to complete the study.

After an overnight fast (from 10 PM the night before) subjects were given a 500 mg (2 x 250 mg) dose of the test or reference formulation and required to thoroughly chew and swallow the two tablets, then rinse and swallow three times with 60 ml of water (total of 180 ml of water) to ensure complete tablet ingestion. Fasting continued for 4½ hours post-dose. Blood samples (7 ml) were collected in Vacutainers (containing EDTA as an anticoagulant) at the following times: 0 (pre-dose), 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0 and 8.0 hours after dosing. The blood samples were then centrifuged and duplicate aliquots of the plasma were transferred to culture tubes and frozen at -18°C until assayed.

There were no reported adverse reactions during the study.

Analytical: [Not for release under FOI]

Since the protocol called for the data of twenty-four subjects to be used in the statistical analysis, the data for subjects #26 and #28 were not used. Subject #27 replaced subject #2 (who dropped from the study prior to its onset), since he was in the same dosing sequence as subject #2.

Results:

The area under the curve (0-t and 0-inf) are practically identical for both the test and reference formulations. Maximum concentration for plasma levels of amoxicillin are similar with <2% difference between the test and reference products.

There are no statistically significant treatment or sequence effects for the major pharmacokinetic parameters.

The 90% shortest confidence intervals for AUC and C_{max} are presented below:

	90% CI
AUC_{0-t}	[96.4; 103.8]
AUC_{inf}	[96.6; 103.5]
C_{max}	[92.7; 103.9]

Since the plasma data for subject #14's first period treatment (Amoxil) may be slightly questionable due to the drug level found in his zero hour sample, the reviewer recalculated the above PK parameters, excluding the data from subject #14. The results are shown below:

	90% CI w/o subj. #14
AUC_{0-t}	[97.3; 104.5]
AUC_{inf}	[97.4; 104.3]
C_{max}	[93.1; 104.7]

The mean plasma levels and pharmacokinetic summary are attached.

In-vitro Dissolution:

Dissolution testing was conducted on the bio-lots of the test and reference products under the following conditions:

USP XXII Apparatus II (paddle) @ 50 rpm
900 ml of water at 37°C ± 0.5°C

Assay:

Waiver Request:

A request for waiver of in-vivo bioavailability study was submitted for the company's 125 mg strength test product based on formulation proportionality with the company's 250 mg strength drug product and comparable dissolution profiles of the 125 mg product vs Amoxil® 125 mg chewable tablet.

The dissolution summaries are appended.

Dissolution testing was also performed for the company's 125 mg chewable tablet vs Amoxil® 125 mg chewable tablet.

Batch Size:

According to the executed batch record, the batch size of the test product used in this bio-study was

Comments:

It should be noted, however, that the USP has no dissolution requirements for this drug product; a disintegration test is performed.

7. If the sponsor wishes to use labeling identical to that of the innovator's product, a small food challenge study should be performed to demonstrate that amoxicillin may be given without regard to meals.

   The study should be a three-way crossover employing 15-18 subjects. The study design should include a fed phase for both the test and reference products and a fasting phase for the test product.

Recommendation:

1. The bioequivalence study conducted by and on its amoxicillin 250 mg chewable tablet is incomplete per comments #1-4 and 7.

   Comments #1-5 and 7 should be transmitted to the company.

P. Lee

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED FPELSOR
FT INITIALED FPELSOR

Concur: Shrikant V. Dighe Date: 11/13/92

Shrikant V. Dighe, Ph.D.
Director, Division of Bioequivalence

JLee/jl/10/14/92

cc: Form 6, #64-031 original, HFD-630 (Hare, OGD), HFD-655 (Pelsor, Lee), HFC-130 (JAllen), HFD-340 (Vish), Drug File

USP XXII Apparatus II Basket ____ Paddle x rpm 50

Medium: water @37°C Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Amoxil® chewable tablet (125 mg & 250 mg)

Assay Methodology: UV absorbance; 272 nm

Results

250 mg

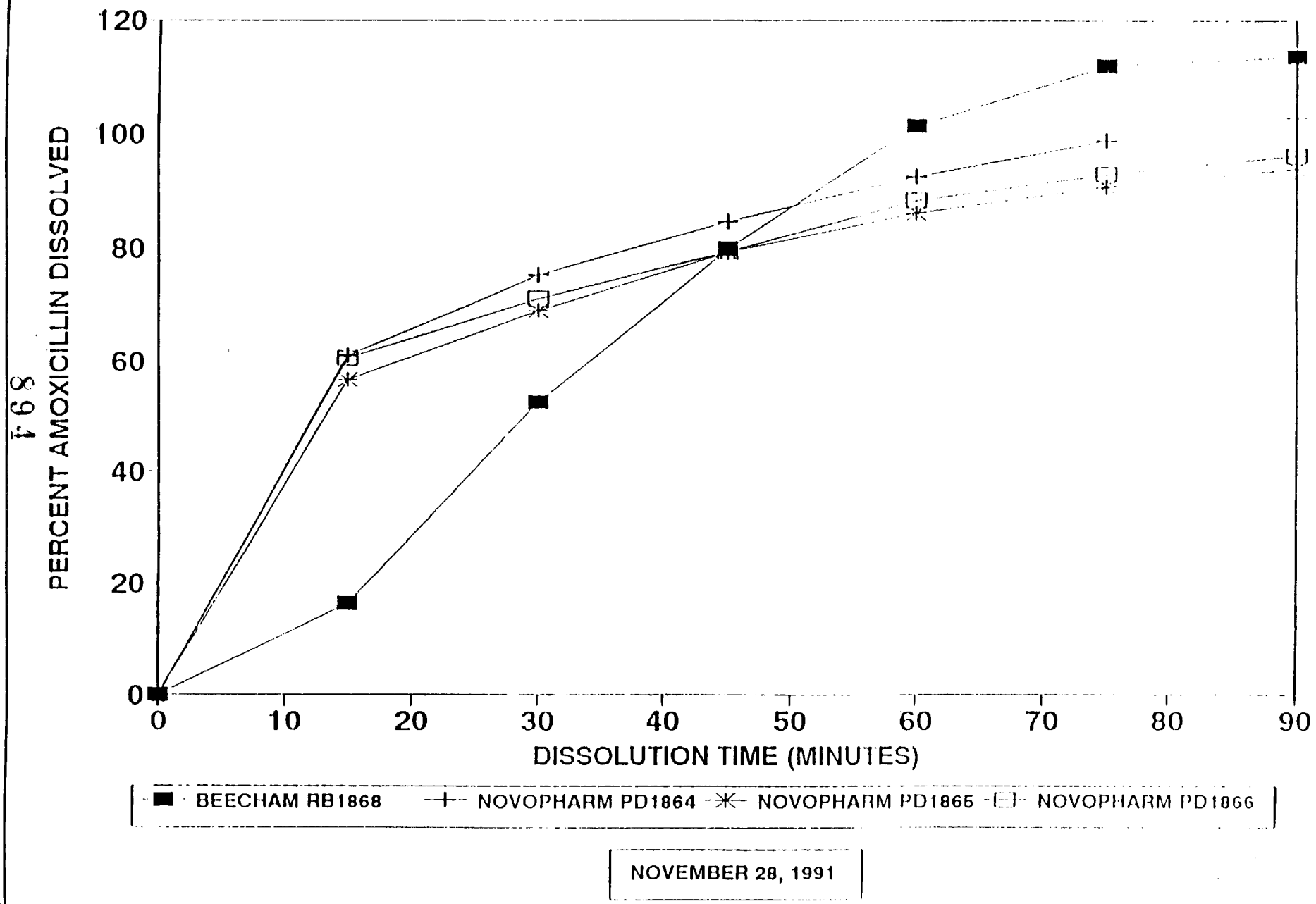
Time (min)	Test Product Lot # PD1867 Mean % Dissolved	Range	(CV)	Reference Product Lot # RH2047 Mean % Dissolved	Range	(CV)
15	54.2		(11.7)	12.0		(20)
30	63.8		(4.7)	37.7		(13)
45	71.2		(5.3)	59.6		(9.7)
60	77.3		(7.6)	78.7		(7.5)
75	82.0		(9.0)	93.9		(4.7)
90	84.7		(9.2)	105.6		(2.6)
			( )			( )

125 mg

	Lot # PD1864			Lot # RB1868		
15	60.8		(6.4)	16.2		(20)
30	75.3		(5.7)	52.4		(15)
45	84.5		(6.0)	79.8		(10)
60	92.3		(6.8)	101.2		(5.3)
75	98.5		(7.5)	111.9		(1.6)
90	102.7		(8.0)	113.4		(1.3)
			( )			( )

AMOXICILLIN CHEWABLE TABLETS 125 mg

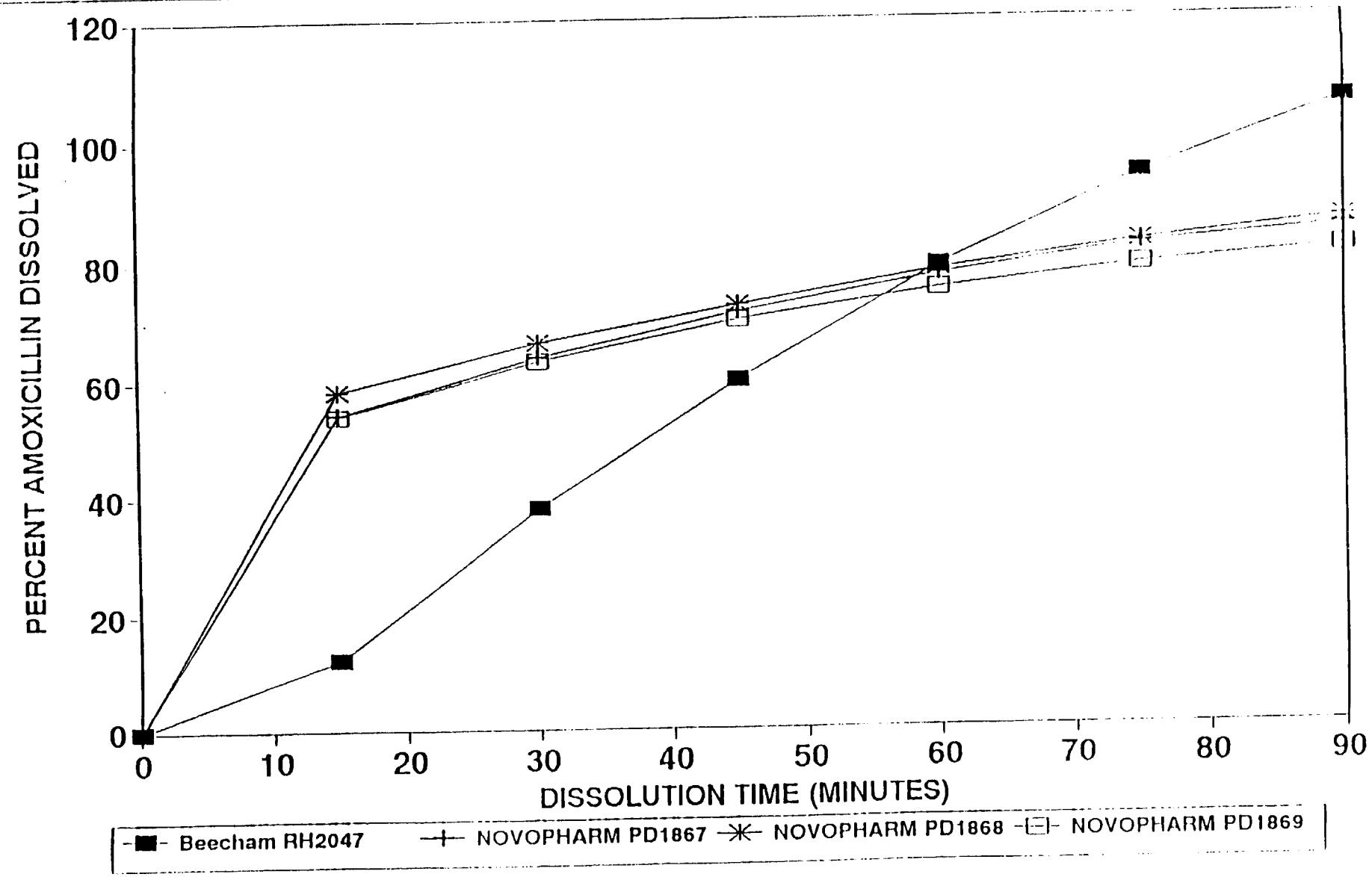
DISSOLUTION PROFILE IN WATER



NOVEMBER 28, 1991

AMOXICILLIN CHEWABLE TABLETS 250mg

DISSOLUTION PROFILE IN WATER



NOVEMBER 27, 1991

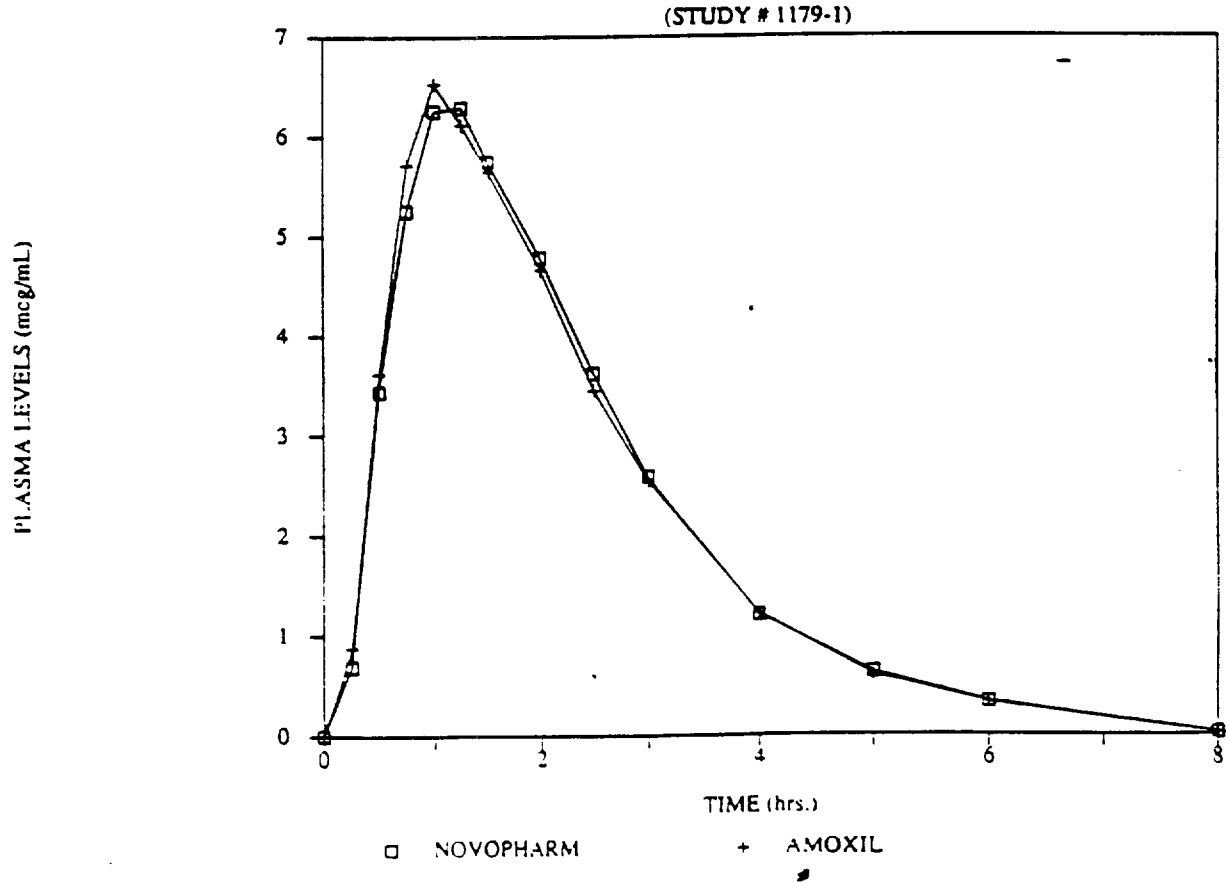
668

STUDY # 1179-1

Mean Plasma Amoxicillin Concentrations (mcg/mL)

Sample Time (Hours)	NOVOPHARM 2 x 250mg	AMOXIL 2 x 250mg
0.00	0.00 ± 0.00	0.00 ± 0.00
0.25	0.69 ± 0.43	0.88 ± 0.62
0.50	3.44 ± 1.43	3.62 ± 1.79
0.75	5.26 ± 1.72	5.72 ± 1.94
1.00	6.26 ± 1.63	6.53 ± 1.84
1.25	6.30 ± 1.43	6.12 ± 1.33
1.50	5.75 ± 1.35	5.65 ± 1.38
2.00	4.79 ± 1.20	4.67 ± 1.30
2.50	3.62 ± 0.91	3.45 ± 1.00
3.00	2.59 ± 0.80	2.54 ± 0.86
4.00	1.20 ± 0.37	1.22 ± 0.45
5.00	0.62 ± 0.21	0.59 ± 0.26
6.00	0.33 ± 0.19	0.33 ± 0.16
8.00	0.03 ± 0.09	0.02 ± 0.08

MEAN PLASMA AMOXICILLIN LEVELS



SUMMARY OF RESULTS

Pharmacokinetic Indices for Plasma Amoxicillin

	Novopharm 2 x 250 mg	Amoxil 2 x 250 mg
AUC (0 - t)(mcg·hr/mL)	15.82 ± 3.00	15.81 ± 3.60
AUC (0 - infinity)(mcg·hr/mL)	16.37 ± 3.07	16.36 ± 3.57
C_{max} (mcg/mL)	6.77 ± 1.46	6.89 ± 1.75
T_{max} (hours)	1.28 ± 0.34	1.13 ± 0.34
$t_{1/2}$ (hours)	1.04 ± 0.16	1.04 ± 0.13
K_{el} (hours^{-1})	0.684 ± 0.108	0.674 ± 0.084

Novopharm vs Amoxicillin

	AUC (0 - t)	AUC (0- infinity)	Cmax
90% Arithmetic C.I.[1]	96.38 - 103.75%	96.61 - 103.54%	92.74 - 103.86%
Power[2]	99.99%	99.99%	99.98%
Westlake's C.L.[3]	4.45%	4.18%	7.44%
Relative Bioavailability[4]	100.06%	100.06%	98.26%

[illegible] confidence interval using Amoxil as the reference

[illegible] power to detect at least a 20% difference between formulations

[illegible]% confidence limit using Westlake's method and Amoxil as the reference

[illegible] calculated using mean parameter values according to the formula: Novopharm / Amoxil(R) x 100%

MAY 12 1993

Amoxicillin Chewable Tablet
125 mg and 250 mg
Form 6, #64-031
Reviewer: J. Lee
640310.593

Novopharm Ltd.
Ontario, Canada
Submission date:
April 26, 1993

Submission of Correspondence

This submission references the bio-study in application #64-031. The bio-study was reviewed (rev.date: 16 Nov 92) and 7 deficiences were conveyed to the sponsor. The analytical laboratory has responded to deficiency #1 (supplying the complete analytical methodology used in the bio-study). Since this is a piece of confidential controlled correspondence that the laboratory has submitted directly to the Agency, the information will be used at a later date in conjunction with the receipt of the rest of the deficiencies.

The Division of Bioequivalence acknowledges receipt of this piece of correspondence.

Recommendation:

No action is indicated from the Division of Bioequivalence at the present time. The Division awaits receipt of the responses to the rest of the deficiencies in the review of the sponsor's bio-study.

J. Lee

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK 5/12/93

JLee/jl/05-10-93

cc: Form 6, #64-031 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Patnaik, Lee), HFC-130 (JAllen), Drug File, Division File

640 E

Amoxicillin (trihydrate)
250 mg Chewable Tablet
AADA 64-031

JAN 28 1994

Therese Ast, Ph.D.
U.S.Agent for:
Novopharm LTD
176 East 71st Street
New York, NY 10021

Dear Ms. Ast:

Reference is made to the *in vivo* bioequivalence study, under fed conditions, submitted on May 6, 1993; and to the information amending your previously submitted study under fasting conditions.

The responses to the fasting study of March 30, 1992 and the final report of your fed study submitted May 6, 1993 have been reviewed by the Office of Generic Drugs/Division of Bioequivalence and we have found them to be incomplete for the following reason:

The laboratory should resubmit the recovery data, calculated as outlined above.

A representative of the Division of Bioequivalence is available to clarify this letter and to assist you with any questions; you may contact Jason A. Gross, Pharm.D., Chief Consumer Safety Officer at (301) 594-0315.

You are required to take an action described under 21 CFR 314.96 which will amend this submission.

All responses and correspondence with regard to this letter should indicate the date of this letter, and be addressed to the Office of Generic Drugs/Division of Bioequivalence, HFD-650.

Sincerely yours,

Shrikant V. Dighe

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

JAN 4 1994

Amoxicillin (trihydrate)
250 mg Chewable Tablet
Form 6, #64-031
Reviewer: J. Lee

Novopharm Ltd.
Ontario, Canada
Submission date:
May 6, 1993

Review of Responses to Comments on Fasting Bio-study and Review of Fed Bio-study

This submission addresses the comments and deficiencies conveyed to the company in the review of their bio-study (sub. date: 3/30/92).

The post-prandial study is reviewed on the following pages.

Review of an in-vivo Bioavailability (fed) Study

Objective:

To assess the relative rate and extent of absorption of two amoxicillin 250 mg chewable tablet formulations under fed conditions.

Study Design:

The clinical study (BP316) was conducted by
under the direction of

Eighteen healthy, non-smoking male volunteers between the ages of 18-45 years and within ± 15% of ideal body weight were successfully screened for this study.

The volunteers had normal findings in the pre-study physical examination and the laboratory tests of hematopoietic, hepatic and renal functions. Those who had a history or presence of significant cardiovascular, hepatic, renal, CNS, hematological or GI disease were excluded as were those with asthma, alcoholism or drug abuse within the previous year, hypersensitivity to amoxicillin, penicillin or the cephalosporins; personality disorders and those who have used nicotine products within the previous 3 months.

The study was designed as a three-way crossover comparing the test product and SmithKline Beecham's Amoxil^{R} 250 mg chewable tablet under fed conditions and to compare the bioavailability of the test product under both fed and fasted conditions. There was a minimum 5 day washout period between phases.

The batches of drug products used in this study are the same ones used in the fasting study.

Drug A - Novopharm 2 x 250 mg amoxicillin chewable tablet, fasted
Drug B - Novopharm 2 x 250 mg amoxicillin chewable tablet, fed
Drug C - SmithKline Beecham 2 x 250 mg Amoxil^{R} (amoxicillin) chewable tablet, fed

The randomization scheme was as follows:

	period 1 1/29/93	period 2 2/4/93	period 3 2/10/93
sequence 1	C	A	B
sequence 2	A	B	C
sequence 3	B	C	A

sequence 1 - subj. #1, 4, 8, 12, 15, 16
sequence 2 - subj. #2, 9, 10, 13, 17
sequence 3 - subj. #3, 6, 7, 11, 14, 18

Of the 18 original enrollees in the study, 3 dropped out before completion of all phases. Subject #6 withdrew before period 2 because of an accident. Subjects #10 and #12 were withdrawn by the attending physician prior to period 2 because of adverse experiences that were probably drug related. Fifteen subjects completed the study.

After an overnight fast, subjects who were in a fed period of the study were given a high-fat breakfast (standard high-fat breakfast recommended by the Division of Bioequivalence) ½ hour before dosing. Those in a fasting period of the study were given a 500 mg (2x250 mg) dose of the test formulation. Subjects were required to thoroughly chew and swallow the tablets with 240 ml of water. Blood samples were collected in Vacutainers containing EDTA at 0 (pre-dose, 2x5 ml) and 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 hours after dosing (1x5 ml). The blood samples were cooled and centrifuged under refrigeration. Plasma samples were then divided in two portions and frozen at -70°C, pending analysis.

All blood draws were taken within 2 minutes of the scheduled time except for subj. #7, 1.25 hour sample in period 1, which was taken 3 minutes late.

There were several protocol deviations of a dietary nature. Those deviations were judged unlikely to affect the bioavailability comparison.

There were several clinical complaints (e.g. headache, itchiness in lower leg, rash) that were reported, most of which were unrelated or only possibly related to the study medication. Two subjects, #10 and #12, had complained of itchiness in the lower leg soon after period 1. The attending physician judged that the complaints were a secondary allergic reaction to amoxicillin and withdrew both subjects from the study.

Analytical: [Not for release under FOI]

Data Analysis and Results:

Plasma level data was analyzed by the SAS General Linear Models Procedure. The samples from the dropout subjects were not analyzed.

The results of the data analysis are shown below:

	(A/B)	(B/C)	(A/C)
AUC_{0-t}	103%	99%	102%
AUC_{inf}	103%	99%	101%
C_{max}	125%	100	124%

A = Novopharm (fasted) B = Novopharm (fed) C = SmithKline (fed)

The germane comparisons are of the test/reference ratios of A/B and B/C. The results show that in a head-to-head comparison of the Novopharm and SmithKline amoxicillin formulations administered after a meal, the mean rate and extent of absorption are comparable. The Novopharm formulation, fasted versus fed, is comparable in extent of absorption; the rate of absorption, however, is decreased by ~25% when the drug product is taken after a meal.

Mean plasma level data and pharmacokinetic indices are attached.

Comment:

3. The company's bio-study (three way crossover) is acceptable.

Recommendation:

1. The responses to the comments and deficiencies contained in the review of the company's fasting bio-study (submission date: March 30, 1992) is incomplete.

2. The company should address comment #1.

   The recommendation and comment #1 should be tansmitted to the company.

R. Lee

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED NTRAN tran 12/23/93
FT INITIALED NTRAN

Concur: N Patnaik Date: 1/4/94

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/09-01-93

cc: Form 6, #64-031 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Tran, Lee), HFD-130 (JAllen), HFD-344 (Vish), Drug File, Division File

TABLE 1

SUMMARY OF RESULTS -- AMOXICILLIN

OBSERVED DATA

MEAN (C.V.%) BIOAVAILABILITY PARAMETERS
(n = 15)

	PARAMETER					
	AUC 0-t (ng.hr/mL)	AUCinf (ng.hr/mL)	Cmax (ng/mL)	tmax (hrs)	Kel (1/hr)	t1/2* (hrs)
TREATMENT:						
NOVOPHARM (Fasted) (A)	26893 (21%)	27718 (20%)	9742 (35%)	1.53 (37%)	0.613 (13%)	1.13
NOVOPHARM (Fed) (B)	26243 (19%)	27170 (19%)	7753 (22%)	1.89 (25%)	0.591 (16%)	1.17
SMITHKLINE B (Fed) (C)	26531 (19%)	27545 (18%)	7844 (20%)	1.68 (35%)	0.587 (15%)	1.18
Ratio of Means (A/B%):	102	102	126			
(B/C%):	99	99	99			
(A/C%):	101	101	124			
p value: (3-way ANOVA)	0.6978	0.7877	0.0036	0.1543	0.5606	
Statistically Significant Differences (LSM):	NS	NS	B C < A	NS	NS	
Detectable Differences						
A vs. B:	8.5%	8.7%	22.5%			
B vs. C:	8.4%	8.5%	22.2%			
A vs. C:	8.4%	8.5%	22.2%			
Power						
A vs. B:	>99.9%	>99.9%	70.1%			
B vs. C:	>99.9%	>99.9%	71.1%			
A vs. C:	>99.9%	>99.9%	71.1%			
Mean of Individual Ratios						
A/B%:	103 (14%)	103 (14%)	125 (23%)			
B/C%:	99 (5%)	99 (5%)	100 (17%)			
A/C%:	102 (14%)	101 (14%)	124 (26%)			
± Westlake 95% Confidence Intervals						
A vs. B:	7.4%	7.1%	38.8%			
B vs. C:	6.2%	6.5%	15.8%			
A vs. C:	6.4%	6.1%	37.2%			
90% Confidence Intervals (Two One-Sided t-Test Method)						
A vs. B:						
lower limit:	97.5%	96.9%	112.5%			
upper limit:	107.4%	107.1%	138.8%			
B vs. C:						
lower limit:	94.0%	93.6%	85.8%			
upper limit:	103.8%	103.6%	111.9%			
A vs. C:						
lower limit:	96.5%	95.6%	111.2%			
upper limit:	106.3%	105.6%	137.2%			

* Mean t1/2 is calculated directly from mean Kel.

TABLE 2

OBSERVED DATA

MEAN (C.V.%) PLASMA AMOXICILLIN CONCENTRATIONS (NG/ML)

AT EACH SAMPLING TIME POINT

(n = 15)

Time (hours)	NOVOPHARM (Fasted) (A)	NOVOPHARM (Fed) (B)	SMITHKLINE B (Fed) (C)	p-value 3-way ANOVA*	Statistically Significant Differences**
PRE-DOSE	0 (N/A)+	0 (N/A)+	0 (N/A)+		
0.5	3284 (39%)	2028 (50%)	2292 (71%)	0.0237	B C < A
0.75	6350 (43%)	3878 (39%)	4373 (49%)	0.0044	B C < A
1	8034 (46%)	5348 (35%)	5901 (37%)	0.0101	B C < A
1.25	8921 (39%)	6312 (30%)	6845 (26%)	0.0041	B C < A
1.5	8546 (33%)	7013 (29%)	7183 (22%)	0.0327	B C < A
2	7582 (25%)	7232 (24%)	6839 (15%)	0.2182	NS
2.5	6666 (25%)	6909 (19%)	6466 (24%)	0.5133	NS
3	5127 (20%)	5897 (19%)	5685 (27%)	0.1207	NS
4	2974 (30%)	3615 (26%)	3806 (28%)	0.0141	A < B C
5	1549 (36%)	2020 (33%)	2084 (32%)	0.0084	A < B C
6	827 (30%)	1123 (41%)	1206 (39%)	0.0019	A < B C
8	200 (101%)	342 (79%)	322 (93%)	0.0526	NS

* The model had treatment, period, sequence and subject (sequence) as factors (see Appendix S2).
** NS = not significant at p=0.05 level. Differences based on the Least Square Means test.
\+ N/A = not applicable.

TABLE D7 18-MAR-93 09:51:59

PROJECT BP316

RATIO ANALYSIS FOR PLASMA AMOXICILLIN AUC 0-t (ng.hr/mL)
OBSERVED DATA

A = NOVOPHARM (Fasted)
B = NOVOPHARM (Fed)
C = SMITHKLINE BEECHAM (Fed)

SUBJECT	A	B	C	A/B%	B/C%	A/C%
1						
2						
3						
4						
5						
7						
8						
9						
11						
13						
14						
15						
16						
17						
18						
MEAN	26893	26243	26531	103	99	102
S.D.	5538	5033	5038	14	5	14
C.V.%	21	19	19	14	5	14

TABLE D8 18-MAR-93 09:51:59

PROJECT BP316

RATIO ANALYSIS FOR PLASMA AMOXICILLIN AUCinf (ng.hr/mL)
OBSERVED DATA

A = NOVOPHARM (Fasted)
B = NOVOPHARM (Fed)
C = SMITHKLINE BEECHAM (Fed)

SUBJECT	A	B	C	A/B%	B/C%	A/C%
1						
2						
3						
4						
5						
7						
8						
9						
11						
13						
14						
15						
16						
17						
18						
MEAN	27718	27170	27545	103	99	101
S.D.	5499	5160	5089	14	5	15
C.V.%	20	19	18	14	5	14

TABLE D9

18-MAR-93 09:51:59

PROJECT BP316

RATIO ANALYSIS FOR PLASMA AMOXICILLIN Cmax (ng/mL)
OBSERVED DATA

A = NOVOPHARM (Fasted)
B = NOVOPHARM (Fed)
C = SMITHKLINE BEECHAM (Fed)

SUBJECT	A	B	C	A/B%	B/C%	A/C%
1						
2						
3						
4						
5						
7						
8						
9						
11						
13						
14						
15						
16						
17						
18						
MEAN	9742	7753	7844	125	100	124
S.D.	3382	1691	1562	28	17	33
C.V.%	35	22	20	23	17	26

OW

SEP 5 1994

Amoxicillin Chewable Tablet
125 and 250 mg
Form 6, #64-031
Reviewer: J. Lee
64031SA.694

Novopharm Ltd.
Ontario, Canada
Submission date:
June 15, 1994

Review of a Study Amendment

This study amendment responds to the deficiency cited in the review of the sponsor's 5/6/93 submission. The deficiency concerned the laboratory's unusual method of calculating 'recovery' in the analytical method. The laboratory was requested to resubmit the recovery data calculated thusly:

The results showed:

Comment:

1. The recovery data calculation is acceptable. All responses to the deficiencies for the fasting and fed studies are now complete and acceptable.

2. In June, 1994, the chemistry reviewer for this application notified the Division of Bioequivalence that there were several problems with the chemistry data and that the sponsor would have to manufacture a new batch of the drug product. Comparative dissolution profiles were requested to be generated [new batch vs bio-batch of sponsor and new batch vs bio-batch of innovator]. That data has not yet been received.

   The Division of Bioequivalence will review that data when it is submitted to the Agency and make a final recommendation at that time.

Recommendation:

The Division of Bioequivalence finds the application incomplete due to comment #2.

Final recommendations will be made when the additional dissolution data is received and assessed.

J. Lee 8/24/94

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED NTRAN
FT INITIALED NTRAN

Concur: _____ Date: 9/5/94

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

JLee/jl/08-23-94

cc: Form 6, #64-031 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Pelsor, Lee), HFC-130 (JAllen), Drug File, Division File

DN

AADA 64-031

FEB 29 1996

Novopharm LTD
Attention: Thérèse Ast, Ph.D., Esq.
Authorized U.S. Agent
4409 Airport Drive N.W.
Wilson, NC 27896

Dear Madam:

Reference is made to your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Amoxicillin Tablets USP, Chewable 125 mg and 250 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JJV

FEB 22 1996

Amoxicillin Chewable Tablet
125 mg & 250 mg
Form 6, #64-031
Reviewer: J. Lee
64031DW.895

Novopharm Ltd.
Ontario, Canada
Submission date:
August 14, 1995

Review of Dissolution Data and a Request for Waiver for a Reformulated Product

Background:

Acceptable bio-studies (fasting & fed) have been conducted on the 250 mg tablet in this application (sub. dates: 3/30/92, 5/6/93, and 6/15/94). In June, 1994, the Division of Bioequivalence was informed that there were several problems with the chemistry data

and that the sponsor would have to manufacture a new batch of the drug product with a revised formulation (major amendment). The chemist assigned to this application requested comparative dissolution profiles to be generated [new batch vs bio-batch of sponsor and new batch vs bio-batch of innovator]. It was agreed that the Division of Bioequivalence would review that data, when submitted, to decide if a new bio-study would be required.

This submission contains the comparative dissolution data outlined above and comparative components and composition data for the product used in the bio-studies and the reformulated product. The sponsor is requesting a waiver of the requirement for in-vivo bioequivalence testing on the proposed reformulation of their 125 and 250 mg test products based on 21 CFR 320.22 (d)(3).

The major changes in the revised formulation is

All dissolution profiles and graphs are appended.

The executed batch records show that the batch size of the reformulated test product is

Comment:

1. The dissolution profiles of the innovator's original and current batches appear similar. The profiles of the sponsor's product show that dissolution is faster with the reformulated product; for the 125 mg strenth product, the dissolution is slightly faster with the reformulation; for the 250 mg strength tablet, the dissolution is markedly faster.

   There is no USP dissolution requirement for this drug product. The dissolution conditions and specification (NLT in 90 min) are a former FDA requirement.

2. From a bioequivalence standpoint the in-vivo performance of the reformulated product is not expected to be altered.

3. Based on the aggregate information contained in this amendment the Division of Bioequivalence agrees that an in-vivo study on the reformulated product is not required.

Final Recommendation:

1. The bioequivalence studies (fasting and fed) conducted by

   for Novopharm Ltd. on its amoxicillin 250 mg chewable tablet, batch #PD 1867, comparing it to Amoxil^{R} 250 mg chewable tablet has been found acceptable by the Division of Bioequivalence. The studies demonstrate that amoxicillin 250 mg chewable tablet is bioequivalent to the reference product, Amoxil^{R} 250 mg tablet, manufactured by SmithKline Beecham.

2. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that amoxicillin 125 mg chewable tablet falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Novopharm's amoxicillin 125 mg chewable tablet is deemed bioequivalent to Amoxil^{R} 125 mg chewable tablet, manufactured by SmithKline Beecham.

3. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and the application is acceptable.

The recommendations and comment #3 should be forwarded to the company.

R. Lee 2/21/96

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK

N. Patnaik 2/21/96

Concur: _____ Date: 2/22/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

JLee/jl/02-15-96

cc: Form 6, #64-031 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFD-130, HFD-344 (Vish), Drug File, Division File

USP XXIII Apparatus II Basket____ Paddle x rpm 50

Medium: water @ 37°C Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Amoxil® 250 mg chewable tablet

Assay Methodology: _____

Results

Novopharm

test date: 8/7/95

Time (min)	Test Product - Current (reformulated) Lot # PD2826 Mean % Dissolved	Range	(CV)	Reference Product - original Lot # PD1867 (bio-batch) Mean % Dissolved	Range	(CV)
15	70.0		(12.4)	57.5		(6.9)
30	80.1		(8.2)	64.5		(5.0)
45	87.3		(5.3)	69.9		(3.5)
60	92.4		(4.2)	74.2		(2.7)
75	96.3		(3.9)	76.8		(2.0)
90	100.0		(3.6)	78.8		(1.6)
____	_____	_____	( )	_____	_____	( )

SmithKline Beecham

test date: 8/7/95	Lot # AC1337 fresh lot exp. 3/96			Lot # RH2047 original lot exp. 4/93 bio-batch		
15	20.6		(14.5)	18.4		(9.8)
30	47.4		(11.2)	47.1		(8.6)
45	70.4		(9.6)	66.9		(6.6)
60	88.3		(7.9)	84.9		(5.0)
75	101.8		(6.1)	97.9		(3.9)
90	109.3		(4.4)	105.9		(3.5)
____	_____	_____	( )	_____	_____	( )

USP XXIII Apparatus II Basket ____ Paddle x rpm 50

Medium: water @37°C Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Amoxil[R] 125 mg chewable tablet

Assay Methodology: ____

Results

Novopharm

test date: 8/8/95

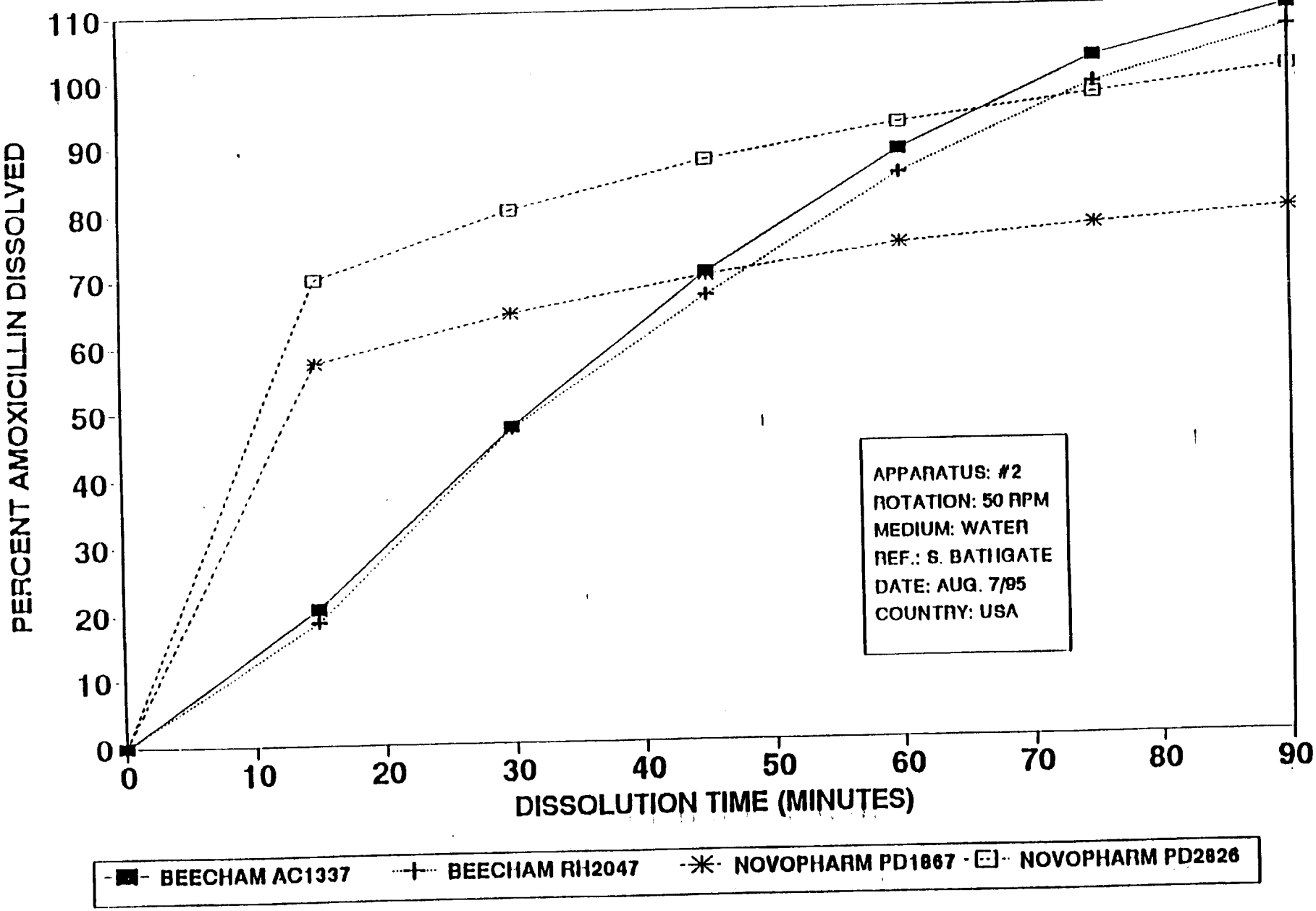
Time (min)	Test Product - Current (reformulated) Lot # PD2786 Mean % Dissolved	Range	(CV)	Reference Product - original Lot # PD1864 Mean % Dissolved	Range	(CV)
15	65.3		(7.3)	58.0		(8.1)
30	72.5		(5.4)	64.7		(3.3)
45	78.2		(3.7)	71.5		(2.9)
60	83.2		(3.1)	77.2		(4.1)
75	86.0		(3.9)	79.6		(3.0)
90	88.5		(3.7)	82.5		(2.7)
____	____	____	( )	____	____	( )

SmithKline Beecham

test date: 8/9/95	Lot # AC1333 fresh lot exp. 3/96			Lot # RB1868 original lot used in sub. exp. 2/93		
15	13.0		(20.9)	21.3		(10.4)
30	38.8		(18.5)	54.4		(11.8)
45	62.2		(9.8)	79.7		(6.2)
60	78.6		(8.7)	95.3		(4.7)
75	92.1		(6.7)	104.7		(3.2)
90	103.4		(3.9)	107.6		(1.6)
____	____	____	( )	____	____	( )

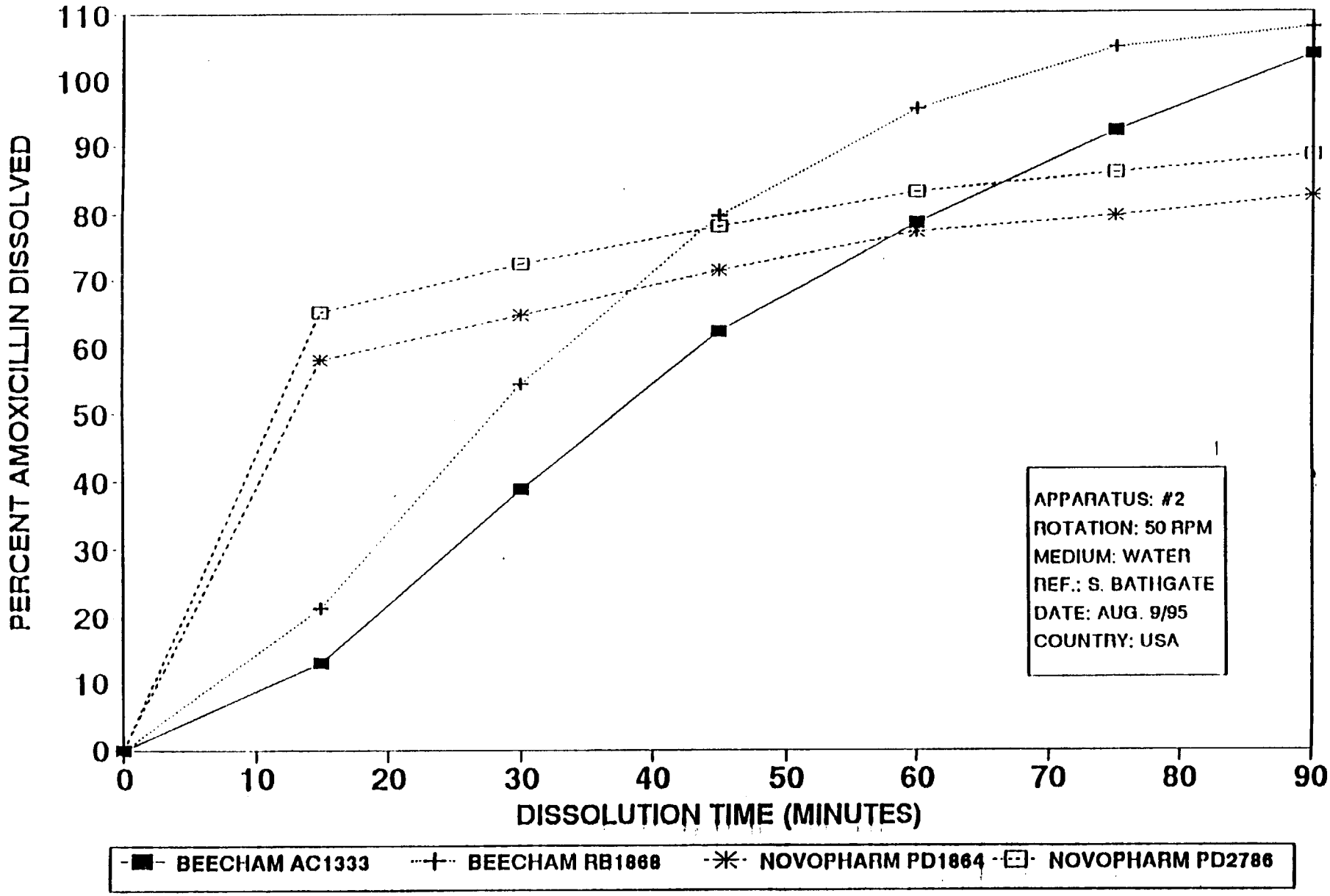
AMOXICILLIN CHEWABLE TABLETS USP, 250MG

DISSOLUTION PROFILE IN WATER



AMOXICILLIN CHEWABLE TABLETS USP, 125MG

DISSOLUTION PROFILE IN WATER



AMOXICILLIN TABLETS USP, CHEWABLE 250 mg

SIDE-BY-SIDE SUMMARY OF DISSOLUTION DATA FOR THE ORIGINAL BATCH, CURRENT BATCH AND REFERENCE PRODUCT

	TEST PRODUCT (Original Biobatch)	TEST PRODUCT (Current Batch)	REFERENCE PRODUCT (Original Biobatch)	REFERENCE PRODUCT (Fresh Lot)
Product Information				
Name	Amoxicillin Tablets, Chewable	Amoxicillin Tablets, Chewable	AMOXIL®	AMOXIL®
Manufacturer	Novopharm Limited	Novopharm Limited	SmithKline Beecham	SmithKline Beecham
Strength	250 mg	250 mg	250 mg	250 mg
Lot Number	PD 1867	PD 2826	RH2047	AC1337
Expiry Date	Nov. 1993	March 1997[2]	April 1993	March 1996
Age of Sample	45 months	5 months	Unknown	Unknown
Dissolution Profile				
Method: A-82				
Results: (mean of 12)				
15 min.	63.8 %	71.9 %	18.4 %	21.3 %
30 min.	72.9 %	80.9 %	47.1 %	48.9 %
45 min.	79.8 %	87.9 %	66.9 %	73.1 %
60 min.	84.6 %	93.0 %	84.9 %	94.4 %
75 min.	87.3 %	96.7 %	97.9 %	106.7 %
90 min.	89.7 %	99.2 %	105.9 %	111.5 %

Note:

1. The above information was summarized from dissolution profile data.
2. Based on the acceptance by the FDA of the proposed two year expiration period, the expiry date for Lot PD 2826 would be March 1997.

AMOXICILLIN TABLETS USP, CHEWABLE 125 mg

SIDE-BY-SIDE SUMMARY OF DISSOLUTION DATA FOR THE ORIGINAL BATCH, CURRENT BATCH AND REFERENCE PRODUCT

	TEST PRODUCT (Original Batch)	TEST PRODUCT (Current Batch)	REFERENCE PRODUCT (Original Lot)	REFERENCE PRODUCT (Fresh Lot)
Product Information				
Name	Amoxicillin Tablets, Chewable	Amoxicillin Tablets, Chewable	AMOXIL®	AMOXIL®
Manufacturer	Novopharm Limited	Novopharm Limited	SmithKline Beecham	SmithKline Beecham
Strength	125 mg	125 mg	250 mg	250 mg
Lot Number	PD 1868	PD 2786	RB1868	AC1333
Expiry Date	Nov. 1993	March 1997[2]	February 1993	March 1996
Age of Sample	45 months	5 months	Unknown	Unknown
Dissolution Profile				
Method: A-82				
Results: (mean of 12)				
15 min.	63.2 %	73.6 %	21.3 %	14.2 %
30 min.	75.1 %	83.1 %	54.4 %	42.8 %
45 min.	84.7 %	90.3 %	79.7 %	67.1 %
60 min.	89.8 %	95.1 %	95.3 %	88.8 %
75 min.	93.3 %	98.7 %	104.7 %	101.5 %
90 min.	96.2 %	101.5 %	107.6 %	109.0 %

Note:

1. The above information was summarized from dissolution profile data.
2. Based on the acceptance by the FDA of the proposed two year expiration period, the expiry date for Lot PD 2786 would be March 1997.